Heart Rate Variability in leucine-rich repeat kinase 2-Associated Parkinson's Disease

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ABSTRACT

Background: Heart rate variability is reduced in idiopathic PD, indicating cardiac autonomic dysfunction likely resulting from peripheral autonomic synucleinopathy. Little is known about heart rate variability in leucine-rich repeat kinase 2-associated PD.

Objectives: This study investigated heart rate variability in *LRRK2*-associated PD.

Methods: Resting electrocardiograms were obtained from 20 individuals with *LRRK2*-associated PD, 37 nonmanifesting carriers, 48 related noncarriers, 26 idiopathic PD patients, and 32 controls. Linear regression modelling compared time and frequency domain values, adjusting for age, sex, heart rate, and disease duration.

Results: Low-frequency power and the ratio of low–high frequency power were reduced in idiopathic PD versus controls ($P < .008$, $P < .029$ respectively). In contrast, individuals with *LRRK2*-associated PD were not statistically different from controls in any parameter measured. Furthermore, all parameters trended toward being higher in *LRRK2*-associated PD when compared with idiopathic PD.

Conclusions: Heart rate variability may remain intact in *LRRK2*-associated PD, adding to a growing literature supporting clinical-pathologic differences between *LRRK2*-associated and idiopathic PD. © 2017 International Parkinson and Movement Disorder Society

Key Words: *LRRK2*; Parkinson's disease; heart rate variability; autonomic dysfunction

Heart rate variability (HRV), variability in heart beat intervals, is governed by autonomic innervation of the heart and derived from a standard electrocardiogram (EKG). HRV assessment allows noninvasive quantification of the activity and balance of the parasympathetic and sympathetic autonomic nervous systems.[1]

Cardiac autonomic dysfunction is prevalent in idiopathic Parkinson's disease (iPD), with reduced HRV as a common feature.[2-8] Reduced ^{123}I-Metaiodobenzylguanidine (^{123}I-MIBG) cardiac uptake is apparent in early PD, indicative of early cardiac sympathetic denervation[9,10] and Lewy pathology has been described in the cardiac plexus in incidental Lewy body disease.[8,11,12] Indeed, the presence of marked cardiac sympathetic denervation with Lewy pathology, in the absence of pathology in the dorsal motor nucleus, in incidental Lewy body disease suggests that cardiac sympathetic denervation may precede the central nervous system degeneration in PD.[12,13]

The proposed early involvement of postganglionic cardiac autonomic nerves in PD, and the simplicity of assessing HRV, suggests potential value as a screening tool for prodromal PD. Several studies have demonstrated reduced HRV in early PD.[14,15] Furthermore, we and others have described significantly reduced HRV in idiopathic rapid eye movement (REM) sleep behavior disorder.[16,17] Finally, a large prospective cohort study found decreased time domain HRV measures were associated with an increased risk of PD.[18] Thus, HRV analysis might make a simple, powerful tool to detect prodromal PD. However, one study found HRV was not predictive of incident PD over 14 years of follow-up.[19] Furthermore, a retrospective cohort study failed

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TABLE 1. Linear regression of time and frequency domain heart rate variability parameters

	Time domain				Frequency domain					
	SDNN		RMSSD		LF		HF		LF/HF	
	Parameter estimate	*P*	Parameter estimate	*P*	Parameter estimate	*P*	Parameter estimate	*P*	Parameter estimate	*P*
iPD vs control	−0.17	.098	−0.05	.639	−0.68	.008	−0.2	.401	−0.48	.029
LRRK2-PD vs control	0.02	.854	0.11	.39	−0.12	.662	0.26	.33	−0.38	.114
LRRK2-PD vs iPD	0.22	.113	0.16	.297	0.72	.068	0.45	.175	0.27	.392
LRRK2-PD vs NMC	0.05	.577	0.06	.524	0.07	.748	0.12	.552	−0.05	.777
NMC vs RNC	0.05	.535	0.06	.509	0.08	.723	0.14	.495	−0.06	.736

All heart rate variability values are log-transformed. Effects were adjusted for sex, age, and mean heart rate; the LRRK2-PD vs iPD comparison was also adjusted for disease duration. SDNN, standard deviation of all normal-to-normal intervals; RMSSD, square root of the mean of the sum of the squares of differences between adjacent normal-to-normal intervals; LF, low frequency; HF, high frequency; iPD, idiopathic Parkinson's disease; LRRK2-PD, LRRK2-associated Parkinson's disease; NMC, nonmanifesting carrier; RNC, related noncarrier.

to associate lower standard deviation of all normal-to-normal intervals or lower square root of the mean of the sum of the squares of differences between adjacent normal-to-normal intervals and PD risk.[20] Finally, age-related changes in HRV may weaken the sensitivity to detect prodromal PD.[21] Clearly, further work in populations at an increased risk of developing PD is required to determine the potential for HRV analysis as a biomarker for prodromal PD.

A pilot study in 10 individuals with leucine-rich repeat kinase 2 (LRRK2)-PD found HRV was not reduced in *LRRK2*-PD, suggesting a relative sparing of cardiac autonomic innervation.[22] This observation is supported by several studies demonstrating relatively preserved cardiac ^{123}I-MIBG uptake in *LRRK2*-PD.[23-27] The present study extends these findings in a larger group of patients to determine whether HRV is altered in *LRRK2*-PD as well as in nonmanifesting carriers and related noncarriers when compared with iPD and unrelated healthy controls.

Methods

Study Participants

Probands with *LRRK2* p.G2019S mutations were identified at Toronto Western Hospital and The Parkinson's Institute, and all family members were invited to participate. iPD patients and healthy individuals (devoid of any neurologic disease or family history of PD) were recruited at Toronto Western Hospital. iPD was defined as individuals with PD, according to clinical diagnosis by a movement disorder specialist, in the absence of a family history of the disease in a first- or second-degree relative. No preset sample size was set for the groups. A total of 20 participants with *LRRK2*-PD (p.P.G2019S), 37 nonmanifesting p.G2019S carriers, 48 related noncarriers, 26 iPD patients, and 32 healthy controls were recruited. The presence or absence of p.G2019S was evaluated in all participants as described previously.[28] The study was performed in accordance with Good Clinical Practice guidelines, including the provision of an informed consent.

EKG Acquisition, Data Retrieval, and Cleaning

In contrast to the longer, more sophisticated ECG acquisition performed in a controlled laboratory environment that has become the gold standard for HRV analysis, we performed a short, relatively uncomplicated bedside analysis of HRV that could be easily performed in clinical practice. Following 5 minutes of inactivity in a supine position, 7-minute resting (supine) 4-lead EKGs (aV_R, aV_L, N, aV_F) were collected during daylight hours in a nonfasting state using a laptop-based cardio-card EKG system (Nasiff Associates, Inc., New York). Data were exported in ASCII format and normal-to-normal (NN) sinus node depolarization intervals were extracted using Physionet WAVE v6.11 (www.physionet.org/) in a Unix environment. Ectopic beats and regions of noise were manually removed. Five minutes of clean NN intervals were imported into Kubios v2.1 (http://kubios.uef.fi.). The following standard time-domain HRV parameters reflecting sympathetic and parasympathetic innervation were calculated from the extracted NN intervals: standard deviation of all NN intervals and square root of the mean of the sum of the squares of differences between adjacent NN intervals. Standard frequency domain parameters were also calculated using fast Fourier transformation: low-frequency power (LF; 0.04-0.15 Hz), high-frequency power (HF; 0.15-0.4 Hz), and the ratio of LF/HF.

Clinical Evaluation

Clinical evaluation included a neurological examination, standardized videotape, and the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Individuals taking anticholinergics, sympathetic agonists, or sympathetic antagonists or with evidence of thyroid dysregulation or diabetes were excluded. Assessments were performed blinded

TABLE 2. Descriptive statistics and heart rate variability values by group

	Healthy control	iPD	*P* value HC vs iPD	LRRK2-PD	*P* value LRRK2-PD vs healthy	*P* value LRRK2 PD vs iPD	Nonmanifesting carrier	*P* value NMC vs LRRK2-PD	RNC	*P* value RNC vs NMC
n	32	26		20			37		48	
% male	44	58	*.18*	75	***.02***	*.28*	70	*.7*	56	*0.18*
Age	59.0 (13.2)	64.2 (10.1)	*.17*	63.6 (13.3)	*.95*	*.2*	49.9	*.3*	49.2	*0.9*
Heart rate	69.4 (11.7)	69.3 (7.4)	***.02***	67.5 (9.4)	*.3*	*.3*	66.2	*.9*	65.0	*0.2*
UPDRSIII	1.6 (1.8)	21.3 (9.6)	***<.0001***	20.3 (10.3)	***<.0001***	*.8*	3.1	***<.0001***	2.4	*0.3*
Disease duration	na	6.2 (5.8)	–	11.5 (6.4)	–	***<.0001***	–	–	–	–
log SDNN[a]	23.6 (10.8)	18.6 (10.1)	–	22.2 (10.3)	–	–	30.32 (14.9)	–	31.6 (16.7)	–
log RMSSD[a]	22 (13.4)	18.3 (10)	–	21.2 (8.7)	–	–	31.5 (19.4)	–	33.9 (21.9)	–
log LF[a]	407 (460.3)	268.2 (528.7)	–	356.3 (415.6)	–	–	521.1 (698.6)	–	595 (762.9)	–
log HF[a]	230.6 (320.4)	135.2 (166.2)	–	164.4 (126.7)	–	–	417.1 (533.3)	–	519.2 (637.5)	–
log LF/HF[a]	3.3 (3.5)	2.4 (2.2)	–	2.3 (2)	–	–	1.6 (1.2)	–	1.7 (1.4)	–

Data are presented as mean (standard deviation) unless noted otherwise. Age and mean heart rate were analyzed using an unpaired *t* test, sex using chi-squared test, disease duration, and UPDRSIII total by Mann–Whitney *U* test. HC, healthy control; iPD, idiopathic Parkinson's disease; LRRK2-PD, LRRK2-associated Parkinson's disease; NMC, nonmanifesting carrier; RNC, related noncarrier; UPDRSIII, Movement Disorders Society Unified Parkinson's Disease Rating Scale part 3; SDNN, standard deviation of all normal-to-normal intervals; RMSSD, square root of the mean of the sum of the squares of differences between adjacent normal-to-normal intervals; LF, low frequency; HF, high frequency; na, not applicable.
[a]HRV parameters were adjusted for age, sex, and mean heart rate. In addition, the LRRK2-PD and iPD groups were adjusted for disease duration. P values <0.05 are highlighted in bold italic text.

to genetic status as described previously.[29] All participants with PD met UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria.[30]

Statistical Analysis

Descriptive statistics for continuous variables were reported as mean (standard deviation) and frequencies (percentages) were reported for categorical variables. We identified 5 group contrasts of interest (Table 1). To adjust for skewness, HRV parameters were log transformed, and the differences between groups were assessed using multivariable linear regression analysis adjusted for age, sex, and mean heart rate. The *LRRK2*-PD versus iPD comparison was also adjusted for disease duration. *P* values were 2-sided, and significance was $P < .05$. Sensitivity analyses that excluded outliers and/or comorbidities had similar inferences and are not shown. The data were analyzed in R statistical software (www.r-project.org version 3.2.2). For unadjusted data, see the Supplemental Table.

Results

Participant Clinical and Demographic Characteristics

LRRK2-PD and iPD patients were of similar age, whereas nonmanifesting family members were younger (Table 2). Disease duration in *LRRK2*-PD was significantly longer than in the iPD group. However, UPDRS-III was similar, suggestive of a similar stage of disease progression (Table 2) and consistent with a large multicenter study, suggesting that *LRRK2*-PD has a more benign symptomatic course than iPD.[31] Information regarding orthostatic hypotension and L-dopa equivalent daily dose was not available for all patients.

Age was significantly associated with all HRV parameters studied other than the LF/HF ratio (all $P < .001$, data not shown). Women had greater variability in HF ($P = .03$) and lower variability in LF/HF ($P = .006$). UPDRS-III was inversely associated with LF/HF in iPD ($P = .042$), but not in *LRRK2*-PD; however, there was no significant association between UPDRS-III and any other HRV parameter studied in either group. Disease duration and smoking were not significantly associated with HRV.

HRV Is Reduced in iPD, But Not in *LRRK2*-PD

The adjusted mean values of the HRV parameters by group are shown in Table 2. Parameter estimates from the multivariable linear regression analyses of each of the 5 HRV measures indicated lower HRV in iPD when compared with healthy controls, which was statistically significant for LF and the LF/HF ratio (Table 1). In contrast, parameter estimates for the

comparison of HRV measures in *LRRK2*-PD and controls did not consistently indicate reduced HRV in *LRRK2*-PD and were not statistically different from controls in any of the 5 HRV outcomes measured. Similarly, there was no significant difference in any outcome measured when individuals with *LRRK2*-PD were compared with nonmanifesting carriers (Table 1). A direct comparison of *LRRK2*-PD to iPD trended toward higher HRV in *LRRK2*-PD across all outcomes.

Nonmanifesting Carriers Had Similar HRV to Related Noncarriers

There was no significant difference between nonmanifesting family members with and without a *LRRK2* mutation in any of the 5 HRV parameters investigated (Table 1).

Discussion

We present evidence that cardiac autonomic innervation is not as consistently affected in PD associated with the G2019S *LRRK2* mutation when compared with iPD.

Reduced HRV is a near universal feature in iPD, with multiple studies demonstrating both sympathetic and parasympathetic involvement. Consistent with previous reports, LF and the LF/HF ratio were reduced in iPD when compared with healthy controls, suggesting a reduced sympathovagal tone.[32] In addition, every other parameter measured trended toward being lower in iPD than healthy controls. In contrast, in *LRRK2*-PD there was no evidence of reduced HRV when compared with healthy controls in any parameter analyzed. The reduced LF and LF/HF in iPD was not evident in *LRRK2*-PD, and individuals with *LRRK2*-PD trended toward having higher HRV than individuals with iPD in all 5 HRV outcomes measured, suggestive of a relatively preserved cardiac sympathetic and vagal tone.

These findings are consistent with several reports that found reduced cardiac ^{123}I-MIBG uptake, typically found in iPD, is attenuated in *LRRK2*-PD.[23-27] In addition, *LRRK2*-PD is associated with less frequent orthostatic hypotension and less sympathetic dysfunction in phase IV of the Valsalva maneuver when compared with iPD.[27] These findings add to a growing literature supporting clinical and pathologic differences between *LRRK2*-PD and iPD.[26,29,33,34] We recently described 2 distinct clinical-pathological subtypes of G2019S-associated PD: 1 with classical Lewy pathology (and a motor-dominant phenotype) and another devoid of brain synucleinopathy (with a broad nonmotor phenotype).[34] Thus, the subtype devoid of brain synucleinopathy may also be devoid of peripheral autonomic synucleinopathy and may not be expected to have diminished HRV. Indeed, the considerable variability in ^{123}I-MIBG uptake in 3 of 6 individuals with *LRRK2*-associated PD is suggestive of subgroups with and without peripheral cardiac autonomic dysfunction.[24]

There was no significant difference in any measure of HRV when *LRRK2*-PD was compared with nonmanifesting carriers, or when nonmanifesting carriers were compared with related noncarriers. Our previous study, reporting on a partially overlapping sample, also noted nonmanifesting family members, regardless of the presence of the mutation, had similar UPDRS scores, constipation, and color discrimination.[29] REM behavior disorder has also been found to be less common in *LRRK2*-PD than iPD.[35] Thus, the prodromal stage of *LRRK2*-PD appears to differ from prodromal iPD. HRV can be added to a list of nonmotor features that may be useful markers of prodromal iPD, but are less promising as potential markers of the prodromal phase of *LRRK2*-PD.

HRV could be useful in the delineation of PD subtypes. Here we find that HRV may distinguish *LRRK2*-PD from iPD. Similarly, HRV has been shown to differentiate individuals with PD with and without concomitant REM sleep behavior disorder[36] and tremor-dominant and akinetic rigid-dominant subtypes.[37]

In conclusion, we report that HRV is not reduced in G2019S-associated *LRRK2*-PD, in contrast to iPD, suggesting that individuals with *LRRK2*-PD may have relatively preserved cardiac autonomic function. Future larger studies, encompassing a broader analysis of sympathetic and parasympathetic features, will be necessary to confirm these results. Given the known neuropathologic heterogeneity of *LRRK2*-PD,[34] the investigation of HRV along with imaging, polysomnography, olfactory testing, and other peripheral biomarkers of the autonomic nervous system (e.g., skin biopsy) may be particularly useful in defining subtypes. ■

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.